PATENT SPECIFICATION

(11) 1 482 238

1 482 238

(21) Application No. 18523/75 (22) Filed 2 May 1975
(31) Convention Application No. CI 1474
(32) Filed 3 May 1974 in
(33) Hungary (HU)
(44) Complete Specification published 10 Aug. 1977
(51) INT CL² C07D 311/36; A61K 31/35, 31/40, 31/44, 31/535; C07D 405/06, 405/12; (C07D 405/06, 295/10); C07D 405/12, 213/53, 311/36)
(52) Index at acceptance
C2C 1341 1530 1532 1562 1673 213 215 220 226 22Y 246 250 251 253 255 25Y 28X 29X 29Y 30Y 313 31Y 323 32Y 339 351 352 360 361 364 36Y 388 43X 440 620 623 624 625 650 652 670 672 760 790 79Y LM TZ

(72) Inventors LASZLO FEUER, ISTVAN DORY, LORAND FARKAS, MIHALY NOGRADI and MARIA POLGAR

(54) IMPROVEMENTS IN ISOFLAVONE DERIVATIVES

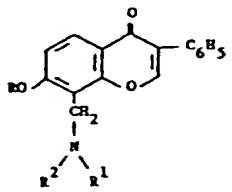
(71) We, CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT., a Hungarian Body Corporate, of 1-5 To-utca, Budapest IV, Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 7-substituted-8-aminomethylisoflavone derivatives and pharmaceutical compositions and animal feeds containing them, as well as to a process for the preparation thereof.

It is now known that 7-alkoxy-isoflavones can be used as animal feed additives owing to their anabolic effects (Hungarian Patent No. 162,377).

7-Alkoxy-isoflavones are naturally occuring organic compounds with high biological activities, which display an important role in the control of the cell metabolism of animal organisms. When administered to the living organism, they exert a significant vitamin-like activity. The practical utilization of these compounds is impeded, however, by the fact that they are completely insoluble in water or aqueous media, and are only sparingly soluble in organic solvents.

The invention relates to 7-substituted-8-aminomethyl-isoflavone derivatives of the general formula (I),



(I)

wherein
R is C_{1-18} alkyl, C_{2-18} alkenyl or C_{7-20} aralkyl,
R^1 is C_{1-4} alkyl, and
R^2 is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, phenyl, pyridyl or picolyl, or
R^1 and R^2 form together with the adjacent nitrogen atom a five- or six-membered heterocyclic ring with one or two hetero atoms (preferably a piperazino, N-methyl-piperazino, morpholino, piperidino or pyrrolidino group),
as well as to their physiologically acceptable salts formed with organic and mineral acids.

In the above formula R represents preferably methyl, ethyl, isopropyl or cetyl.

The C_{1-10} alkyl group may be straight-chained or branched. The C_{2-18} alkenyl group is preferably vinyl, allyl, butenyl or octadecenyl, whereas the C_{7-9} aralkyl group is preferably benzyl or β-phenethyl.

A particularly preferred representative of the C_{1-4} hydroxyalkyl groups is hydroxyethyl.

Preferred compounds having the general formula (I) are those wherein R is methyl, isopropyl or cetyl, R^1 is methyl or butyl, and R^2 is methyl, α-picolyl, α-methyl, β-hydroxyethyl or β-hydroxyethyl, or R^1 and R^2 form together with the adjacent nitrogen atom a morpholino, pyrrolidino or piperidino group, or a physiologically acceptable salt thereof.

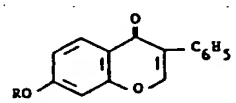
The compounds having the general formula (I) most preferred for pharmacological or veterinary use are as follows:
7-methoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone,
7-methoxy-8-morpholinomethyl-isoflavone,
7-isopropoxy-8-morpholinomethyl-isoflavone,
7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone,
7-isopropoxy-8-piperidinomethyl-isoflavone,
7-isopropoxy-8-[*n*-butyl-(2-methylpyrid-6-yl)-aminomethyl]-isoflavone,
7-isopropoxy-8-pyrrolidinomethyl-isoflavone,
7-cetyloxy-8-morpholinomethyl-isoflavone,
and the physiologically acceptable salts of the above compounds.

As mentioned above, the compounds of the general formula (I) form salts with organic or mineral acids. Of the salts the hydrochlorides, hydrosulfates, nicotinates, bitartrates, citrates, glyconates and lactates are to be mentioned.

The organic or mineral acid addition salts of the compounds having the general formula (I) crystallize from aqueous solvents with the uptake of crystal water. 4 to 5% aqueous solutions can be formed from the hydrochlorides thus obtained, whereas from the salts formed with organic acids 0.5 to 1% aqueous solutions can be prepared. More concentrated aqueous solutions can be prepared by adding 5 to 10% of an alcohol, glycerine, or 4 to 5% of glucose to the solvent.

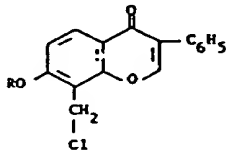
The compounds of the general formula (I) can be prepared according to the invention as follows:

a) a compound of the general formula (II),



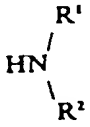
(II)

wherein R has the same meanings as defined above, is subjected to chloromethylation, and the obtained compound of the general formula (III),



(III)

wherein R has the same meanings as defined above, is reacted with a secondary amine of the general formula (IV),



(IV)

wherein R^1 and R^2 each have the same meanings as defined above; or

b) a compound of the general formula (III), wherein R has the same meanings as defined above, is reacted with an amine of the general formula (IV), wherein R^1 and R^2 each have the same meanings as defined above.

If desired, the compounds of the general formula (I) so obtained can be converted into their physiologically acceptable acid addition salts formed with organic or mineral acids.

The starting substances of the general formula (II) are known compounds and can be prepared as described in Hungarian Patent No. 162,377.

In the first step of process variant a) a 7-alkoxyisoflavone of the general formula (II) is subjected to chloromethylation. The reaction may be performed with dry gaseous hydrochloric acid in the presence of paraformaldehyde, or with concentrated aqueous hydrochloric acid in the presence of formaldehyde. The chloromethylation is conducted preferably in the presence of a Lewis acid, such as zinc chloride, aluminium chloride or stannic chloride. As reaction medium e.g. acetic acid or propionic acid can be used. The reaction is performed generally at 60 to 100°C, preferably at 85 to 95°C.

The compounds of the general formula (III) so obtained can be isolated in a known way, e.g. by concentrating the reaction mixture and precipitating the product with concentrated hydrochloric acid.

The compounds of the general formula (III) can be converted into the desired end-products of the general formula (I) by reacting them with a secondary amine of the general formula (IV). As amine reactant of the general formula (IV) preferably β-methylamino-ethanol, morpholine, piperidine, pyrrolidine, or 2-n-butylamino-6-methylpyridine can be used. The reaction is suitably carried out at elevated temperatures, preferably at the boiling point of the reaction mixture. As reaction medium preferably an alkanol of 1—4 carbon atoms, such as methanol, ethanol or propanol, or an excess of the amine of the general formula (IV) can be used. The excess of the amine also serves as acid binding agent to bind the hydrochloric acid liberated in the reaction.

The compounds of the general formula (I) so obtained can be isolated in known manner, preferably by pouring the mixture into water, removing the solvent, and, if necessary, precipitating the product from the residue.

The compounds of the general formula (I) can be converted into their acid addition salts in known manner e.g. by reacting them with a preferably stoichiometric amount of the appropriate acid in a solvent medium (such as in an alkanol, e.g. in methanol or ethanol).

The compounds of the general formula (I) are of interest for the therapy of osteopathic conditions (i.e. for the treatment of cardiac and pulmonary disorders connected with hypoxia and hypercapnia, such as cor pulmonale, angina pectoris, emphysema and pulmonary fibrosis), and for the treatment of peripheral blood supply disorders. These compounds exert, on the one hand, a favourable (oxygen-separating) effect on the oxidative phosphorylation and energy-preserving processes, and, on the other hand, they influence the energy-intensive ion translocation processes (Ca circulation and mineralization) at a subcellular mitochondrial level.

The 8-aminomethyl derivatives increasing significantly the mitochondrial cytochrome-C enzyme activity.

Compared to many other 7-alkoxy-isoflavone compounds, the new 8-aminomethyl derivatives have the advantage that they are water-soluble.

The invention provides in another aspect animal feeds, watering compositions or feed additives containing as active ingredient a compound of the general formula (I) or a physiologically acceptable salt thereof. These animal feeds or feed additives are prepared by adding a compound of the general formula (I) or a physiologically acceptable salt thereof to the animal feed, or by admixing a compound of the general formula (I) or said salt thereof with an appropriate physiologically acceptable solid or liquid carrier or comestible. Preferred compounds are those listed hereinbefore. Thus our invention extends to a method of increasing the weight gain of livestock which comprises administering to said livestock an anabolically effective amount of a compound of the invention.

A still further aspect of our invention provides pharmaceutical compositions containing as active ingredient a compound of the general formula (I) or a physiologically acceptable salt thereof in admixture with a pharmaceutically acceptable solid or liquid carrier, diluent and/or auxiliary agent.

The pharmaceutical compositions may be prepared according to conventional methods of pharmacy.

If desired, the compounds of the general formula (I) can be admixed with other additives. As additives e.g. biologically active substances, such as vitamins, amino acids, choline chloride, salts of mineral acids, trace elements and other known biologically active substances can be used. The feed additives can be marketed preferably in the form of premixes containing the compounds of the general formula (I) or their salts in admixture with other biologically active

components. Furthermore, diluents, solvents, lubricants, carriers and formulating agents can also be admixed with the active agents. The feed additives can be admixed with the animal feed in the form of for example powders, powder mixtures, granulates, solutions, emulsions or suspensions. The compositions containing the compounds of the general formula (I) can also be admixed with the drinking water of the animals.

For use in human therapy, the compounds of the general formula (I) or their salts may be converted to pharmaceutical compositions, such as tablets, coated tablets, powder mixtures, solutions, emulsions or suspensions, preferably for oral administration. Compositions in unit dosage form are often preferred. The pharmaceutical compositions usable in human therapy as well as the dietetic products may contain, in addition to the active agent of the general formula (I) or a salt thereof, other biologically active substances, primarily vitamins, as well. The compounds of the general formula (I) or their salts are preferably formulated into tablets weighing 100 to 200 mg. These tablets may contain conventional additives (such as talc, starch or magnesium stearate) in addition to the active agent. The daily dosage varies depending on the prescription of the physician and the condition of the patient.

The biological effects of the compounds having the general formula (I) are evident from the results of the following tests:

Pharmacological and clinical studies

When administered to rats for 5 weeks in an oral dosage of 10 mg./kg./day, 7-isopropoxy-8-morpholinomethyl-isoflavone nicotinate caused a significant nitrogen retention. In a 45 days' swimming test performed on male rats, a daily oral dosage of 5 mg./kg. of the above compound increased significantly the swimming performance of the animals.

The above compound decreased significantly the oxygen demand of resting rats. In this test the animals were treated with a daily dosage of 1 mg./100 g. body weight for 4 weeks.

The compounds according to the invention increase significantly calcium, phosphate and potassium retention. Neither oestrogenic, nor androgenic side effects were seen in our tests, and the compounds were not seen to influence the functions of the thyroid gland and adrenal cortex, either. The activity of the glycolytic enzyme system increases upon the administration of the compounds. The compounds appear to act on the oxidation of the NAD-dependent substrates in such a way that they decrease the intensity of oxidation in the resting state, but increase the intensity of oxidation in the activated state. The compounds exert a stimulating effect on the shuttle mechanism, and improve the efficiency of oxidation (i.e. they increase the energy-intensive swelling of mitochondria and the activity of α-glycerophosphate).

The tested compounds were seen to increase the oxidation capacity of all liver mitochondrium substrates (the measurements were carried out in a Warburg apparatus).

Weight gain increasing effects:

When admixed with animal feed in a concentration of e.g. 2 g./100 kg., the compounds according to the invention effectively increase the weight gain of farm animals.

The tests were carried out on groups consisting of 30 castrated cocks each. The test period lasted for 35 days. The compounds under examination were admixed with the feed in a concentration of 2 g./100 kg. of feed. In the pre-treatment period (one week) as well as in the first week of the test period the animals were fed with starting feed, and thereafter feeding was continued with fattening feed. The compositions of these feeds were as follows:

Starting feed: corn: 60.0%, 45% soybean: 20.0%, alfalfa meal: 2%, 65% fish meal: 10.0%, yeast: 3.3%, calcium phosphate: 0.6%, lime: 2.3%, salt: 0.3%, vitamin premix I: 1.0%, mineral premix I: 0.5%.

Fattening feed: corn: 50.0%, wheat: 14.9%, 45% soybean: 12.5%, peanut grits: 9.0%, alfalfa meal: 2.0%, 65% fish meal: 4.5%, meat meal (45%): 3.0%, calcium phosphate: 1.0%, lime: 1.8%, salt: 0.3%, vitamin premix II: 0.5%, mineral premix I: 0.5%.

The compositions of the vitamin premixes utilized were as follows:

Test No.	Compound	Increase of weight gain, related to the controls
I	—(control)	—
	Compound "A"	+5.74%
	Compound "B"	+8.71%
	Compound "C"	+4.39%
II	—(control)	—
	Compound "A"	+7.51%
	Compound "B"	+5.54%
III	—(control)	—
	Compound "A"	+6.81%
	Compound "B"	+4.34%
IV	—(control)	—
	Compound "A"	+8.76%
	Compound "B"	+4.58%

Compound "A": 7-isopropoxy-8-morpholinomethyl-isoflavone nicotinate
Compound "B": 7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)isoflavone nicotinate
Compound "C": 7-methoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone nicotinate

The invention is elucidated in detail by the aid of the following non-limiting Examples.

Example 1.

7-Methoxy-8-chloromethyl-isoflavone.

24.0 g. of paraformaldehyde are added to a suspension of 50.4 g. of 7-methoxy-isoflavone in 500 ml. of glacial acetic acid, and the mixture is heated to 90°C. A mixture of 1.5 g. of zinc chloride and 150 ml. of concentrated hydrochloric acid is added dropwise to the obtained solution within 2 hours, and the mixture is heated for further 2 hours at 90 to 95°C. The mixture is clarified with 1.0 g. of charcoal, and filtered. The filtrate is evaporated under reduced pressure to a final volume of 100 ml., and 20 ml. of concentrated hydrochloric acid are added to the residue. The mixture is cooled in ice bath, the separated crystals are filtered off, washed with 80% acetic acid, and dried *in vacuo*. The obtained 51.8 g. of crude product is recrystallized from hot methanol to obtain purified 7-methoxy-8-chloromethyl-isoflavone, m.p.: 146—148°C.

Example 2.

7-Methoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone

8 ml. of β-methylamino-ethanol are added to a suspension of 15.0 g. of 7-methoxy-8-chloromethyl-isoflavone in 150 ml. of methanol, and the mixture is boiled for 3 hours. The obtained solution is poured into 450 ml. of water, and the aqueous mixture is cooled. the separated product is filtered off, washed with 20% aqueous methanol, and dried. 15.2 g. of the title compound are obtained; m.p.: 72—74°C (after recrystallization from methanol).

Example 3.

7-Methoxy-8-morpholinomethyl-isoflavone and salts

35 ml. of morpholine are added to a suspension of 60.0 g. of 7-methoxy-8-chloromethyl-isoflavone in 600 ml. of methanol, and the mixture is heated to

boiling with stirring. The solids dissolve within 20 minutes. After 3 hours of boiling the slightly yellowish solution is poured into 2400 ml. of water with stirring. The mixture is cooled, the separated precipitate is filtered off, washed with 20% aqueous methanol, and dried. 67.1 g. of 7-methoxy-8-morpholinomethyl-isoflavone are obtained; m.p.: 179—180°C (after recrystallization from methanol).

7-Methoxy-8-morpholinomethyl-isoflavone hydrochloride

17.5 g. of 7-methoxy-8-morpholinomethyl-isoflavone are suspended in 160 ml. of absolute methanol, and the suspension is heated to boiling with stirring. A mixture of 5 ml. of concentrated hydrochloric acid and 15 ml. of methanol is added to the suspension, whereupon the solids dissolve completely. After 15 minutes of boiling the mixture is clarified with charcoal, filtered when hot, the filtrate is diluted with 15 ml. of benzene, and 66% of the solvents are distilled off under atmospheric pressure. The obtained residue is cooled to −10°C, the separated salt is filtered off, washed with methanol and dried. 16.9 g. of 7-methoxy-8-morpholinomethyl-isoflavone hydrochloride are obtained; m.p.: 240—242°C.

7-Methoxy-8-morpholinomethyl-isoflavone nicotinate

14.0 g. of 7-methoxy-8-morpholinomethyl-isoflavone are dissolved in 140 ml. of hot abs. isopropanol, and a suspension of 5.0 g. of nicotinic acid in 15 ml. of isopropanol is added to the solution. The slightly yellowish solution is boiled for 15 minutes, thereafter it is cooled to crystallize the product. The product is filtered off at −10°C and washed with isopropanol. After drying 18.3 g. of 7-methoxy-8-morpholino-methyl-isoflavone-nicotinate are obtained. M.p.: 157—158°C (after recrystallization from 85% isopropanol).

Example 4.

7-Isopropoxy-8-chloromethyl-isoflavone

56.0 g. of 7-isopropoxy-isoflavone are dissolved in 560 ml. of acetic acid under gentle heating. 24 g. of paraformaldehyde are added to the solution, the mixture is heated to 90°C, and a mixture of 1.5 g. of zinc chloride and 150 ml. of concentrated hydrochloric acid is added dropwise to the stirred mixture at 90—95°C, under constant stirring. The mixture is maintained at 90—95°C for one additional hour, thereafter it is clarified with charcoal, filtered when hot, and the filtrate is evaporated under reduced pressure to a final volume of 150 to 160 ml. 20 ml. of concentrated hydrochloric acid are added to the residue, and the mixture is cooled in an ice bath with stirring. The separated crystals are filtered off, washed with 80% acetic acid, and dried. 50.6 g. of the title compound are obtained; m.p.: 125—126°C.

Example 5.

7-Isopropoxy-8-morpholinomethyl-isoflavone and salts

A mixture of 32.8 g. of 7-isopropoxy-8-chloromethyl-isoflavone, 164 ml. of absolute alcohol and 20 ml. of morpholine is heated to boiling, and the obtained solution is boiled for 3 hours. The hot solution is poured very slowly into 700 ml. of stirred water. The separated crystals are filtered off after cooling, and washed with 20% aqueous alcohol. After drying 37.7 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are obtained. M.p.: 126—128°C (after recrystallization from methanol).

7-Isopropoxy-8-morpholinomethyl-isoflavone hydrochloride monohydrate

10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are dissolved in 50 ml. of hot absolute ethanol, and a mixture of 2.8 ml. of concentrated hydrochloric acid and 10 ml. of absolute alcohol is added. After 0.5 hour of boiling the mixture is clarified with activated carbon, filtered, and the filtrate is cooled. The separated substance is filtered off and washed with 96% alcohol. After drying, 10.1 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone hydrochloride monohydrate are obtained; m.p.: 223—224°C.

7-Isopropoxy-8-morpholinomethyl-isoflavone hydrosulphate

A mixture of 1.45 ml. of concentrated sulfuric acid (d = 1.84) and 10 ml. of methanol is added dropwise to a warm solution of 10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone in 40 ml. of methanol, and the mixture is boiled for 0.25 hour. During this period the crystalline end-product starts to separate. The mixture is cooled with stirring, immersed into an ice bath, the separated crystals are filtered off, washed with absolute methanol, and dried at 60°C. 9.9 g. of 7-

isopropoxy-8-morpholinomethyl-isoflavone hydrosulfate are obtained; m.p.: (195)—228—230°C.

7-Isopropoxy-8-morpholinomethyl-isoflavone nicotinate

10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are dissolved in 40 ml. of hot isopropanol, and a suspension of 3.5 g. of nicotinic acid in 10 ml. of isopropanol is added to the solution. The reaction mixture is boiled for 15 minutes, then activated carbon is added to the mixture, and boiling is continued for additional 0.5 hours. The mixture is filtered, the filtrate is cooled to −10°C, the separated crystals are filtered off, washed with isopropanol and dried in a vacuum desiccator. 11.5 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone nicotinate are obtained; m.p.: 133—134°C.

When 7-isopropoxy-8-morpholinomethyl-isoflavone is recrystallized from a fourfold amount of 85% isopropanol, the compound absorbs one mole of crystal water, and retains this crystal water even after drying in a desiccator. 7-Isopropoxy-8-morpholinomethyl-isoflavone nicotinate monohydrate melts at 106—108°C.

7-Isopropoxy-8-morpholinomethyl-isoflavone bitartrate hydrate

10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are dissolved in 40 ml. of hot isopropanol, and a suspension of 4.0 g. of tartaric acid in 10 ml. of isopropanol is added to the stirred solution. After some seconds the end-product rapidly starts to crystallize. After 15 minutes of boiling the mixture is cooled, the crystals are filtered off, washed with isopropanol and dried. 13.3 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone bitartrate hydrate are obtained; m.p.: 184—186°C.

7-Isopropoxy-8-morpholinomethyl-isoflavone citrate hydrate

10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are dissolved in 50 ml. of hot 85% isopropanol, and a suspension of 6.5 g. of citric acid in 15 ml. of 85% isopropanol is added. After 15 minutes of boiling the obtained clear solution is diluted with 10 ml. of dry benzene, and 20 ml. of the volatile components are distilled off under atmospheric pressure. The residual solution is clarified with charcoal, filtered, and stirred to initiate crystallization. The crystal-containing mixture is cooled with ice, the crystals are filtered off, washed with dry isopropanol, and dried. 14.1 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone citrate hydrate are obtained; m.p.: 151—153°C.

7-Isopropoxy-8-morpholinomethyl-isoflavone gluconate

10.0 g. of 7-isopropoxy-8-morpholinomethyl-isoflavone are dissolved in 50 ml. of dry warm isopropanol, and 10 ml. of a 50% aqueous gluconic acid solution are added. The mixture is boiled for 0.5 hours, and the obtained solution is concentrated, whereupon the product starts to separate. The concentrate is cooled, the separated crystals are filtered off, washed with ice-cold 85% isopropanol, and dried at 60°C. 15.5 g. of snow-white, crystalline 7-isopropoxy-8-morpholinomethyl-isoflavone gluconate are obtained; m.p.: 131—133°C.

Example 6.

7-Isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone and salts

A mixture of 20.0 g. of 7-isopropoxy-8-chloromethyl-isoflavone, 16 ml. of β-methylaminoethanol and 100 ml. of absolute ethanol is refluxed for 6 hours. The light yellow solution is clarified with charcoal, filtered, and the filtrate is evaporated to dryness in vacuo. The obtained 31.0 g. of resinous substance is stirred with 31 ml. of 50% aqueous acetone, the pH of the mixture is adjusted to 8 with concentrated hydrochloric acid, finally the mixture is cooled to −10°C. The separated crystals are filtered off, washed with 50% aqueous acetone, and dried in a desiccator. 21.7 g. of 7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone are obtained; m.p.: 80—81°C.

7-Isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone hydrochloride monohydrate

10.0 g. of 7-isopropoxy-8-chloromethyl-isoflavone are reacted with 8 ml. of β-methylaminoethanol in 50 ml. of absolute ethanol as described in Example 5. The reaction mixture is evaporated to dryness, the obtained 15 g. of resinous residue are dissolved in 100 ml. of hot 1 N hydrochloric acid, and the product is precipitated by salting out with 12.0 g. of sodium chloride. The mixture is cooled,

the separated crystals are filtered off, dried, and recrystallized from a twofold amount of methanol. 6.4 g. of 7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone hydrochloride monohydrate are obtained; m.p.: (78)—164—166°C.

7-Isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone nicotinate

30.0 g. of 7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone are dissolved in 90 ml. of hot isopropanol, and a suspension of 10.2 g. of nicotinic acid in 32 ml. of isopropanol is added. After 15 minutes of boiling the mixture is cooled to −10°C with stirring. The separated crystals are filtered off, washed with isopropanol, and dried in a vacuum desiccator. 26.0 of 7-isopropoxy-8-(methyl-β-hydroxyethylamino)-methyl-isoflavone nicotinate are obtained; m.p.: 120—121°C.

7-Isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone bitartrate hydrate

10.0 g. of 7-isopropoxy-8-(methyl-β-(hydroxyethyl-aminoethyl)-isoflavone are dissolved in 40 ml. of hot isopropanol, and a suspension of 4.1 g. of tartaric acid in 10 ml. of isopropanol is added. The mixture is boiled for 0.25 hour; during this operation the end-product starts to crystallize. After cooling the crystals are filtered off, washed with isopropanol and dried. 12.6 g. of 7-isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone bitartrate hydrate are obtained; m.p.: 134—136°C.

Example 7.

7-Isopropoxy-8-piperidinomethyl-isoflavone and its nicotinate

A mixture of 10.0 g. of 7-isopropoxy-8-chloromethyl-isoflavone, 50 ml. of absolute ethanol and 10 ml. of piperidine is refluxed for 6 hours. The solution is clarified with charcoal, filtered, and the filtrate is cooled to −10°C. The separated crystals are filtered off, washed with absolute ethanol, and dried at 60°C. 9.06 g. of 7-isopropoxy-8-piperidinomethyl-isoflavone are obtained; m.p.: 138°C.

7-Isopropoxy-8-piperidinomethyl-isoflavone nicotinate monohydrate

3.8 g. of 7-isopropoxy-8-piperidinomethyl-isoflavone are dissolved in 15 ml. of hot isopropanol, and a suspension of 1.3 g. of nicotinic acid in 5 ml. of 85% isopropanol is added to the stirred solution. After 0.5 hours of boiling the mixture is cooled, the separated crystals are filtered off, washed with 85% isopropanol, and dried in a desiccator. 4.4 g. of 7-isopropoxy-8-piperidinomethyl-isoflavone nicotinate monohydrate are obtained; m.p.: 133—134°C.

Example 8.

7 - Isopropoxy - 8 - [n - butyl - (2 - methylpyrid - 6 - yl) - aminomethyl] - isoflavone hydrochloride

A mixture of 10.0 g. of 7-isopropoxy-8-chloromethylisoflavone, 50 ml. of absolute alcohol and 6 ml. of 2-n-butylamino-6-methylpyridine is refluxed for 2 hours. The mixture is clarified when hot with activated carbon, filtered, and the filtrate is evaporated to dryness *in vacuo*. The 16.7 g. of resinous substance are dissolved in 33 ml. of acetone, the solution is acidified strongly with concentrated hydrochloric acid, and diluted with water to effect crystallization. After cooling the crystals are filtered off, washed with aqueous acetone, and dried in a vacuum desiccator. 8.6 g. of the title compound are obtained; m.p.: 108—110°C (after recrystallization from methanol).

Example 9.

7-Isopropoxy-8-pyrrolidinomethyl-isoflavone and salts

5 ml. of pyrrolidine are added to a suspension of 10.0 g. of 7-isopropoxy-8-chloromethyl-isoflavone in 50 ml. of abs. ethanol, and the mixture is refluxed for 3 hours (the solids dissolve even at 50°C). The orange solution is clarified with charcoal, filtered, and 100 ml. of water are added to the warm filtrate. The product is isolated as described in Example 5. 10.5 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone are obtained; m.p.: 115—116°C.

7-Isopropoxy-8-pyrrolidinomethyl-isoflavone hydrochloride hydrate

A mixture of 2.5 ml. of concentrated hydrochloric acid (d = 1.19) and 10 ml. of absolute ethanol is added to a warm solution of 10.0 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone in 38 ml. of absolute ethanol, and the obtained mixture is

boiled for 0.25 hour. The crystals which separate upon cooling are isolated as described in the second paragraph of Example 5. 10.25 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone hydrochloride hydrate are obtained; m.p.: 218—220°C.

7-Isopropoxy-8-pyrrolidinomethyl-isoflavone nicotinate

10.0 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone are dissolved in 30 ml. of warm dry isopropanol, and a suspension of 3.4 g. of nicotinic acid in 10 ml. of dry isopropanol is added. After 15 minutes of boiling the reaction mixture is processed as described in the fourth paragraph of Example 5. 12.60 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone nicotinate are obtained; m.p.: 156—158°C.

7-Isopropoxy-8-pyrrolidinomethyl-isoflavone bitartrate hydrate

A suspension of 4.0 g. of tartaric acid in 10 ml of 85% isopropanol is added with stirring to a hot solution of 10.0 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone in 40 ml. of isopropanol. The crystals immediately begin to separate. After 0.5 hour of boiling the mixture is cooled, the crystals are filtered off, washed with cold 85% isopropanol, and dried at 60°C under atmospheric pressure. 14.30 g. of 7-isopropoxy-8-pyrrolidinomethyl-isoflavone bitartrate hydrate are obtained; m.p.: 166—168°C.

Example 10.

7-Cetyloxy-8-chloromethyl-isoflavone

23.0 g. of 7-cetyloxy-isoflavone and 6.0 g. of paraformaldehyde are dissolved in 460 ml. of warm glacial acetic acid. A mixture of 0.4 g. of zinc chloride and 40 ml. of concentrated hydrochloric aicd is added to the solution at 90 to 95°C within 2 hours, and the mixture is stirred for additional 2 hours at 90 to 95°C. The mixture is clarified with activated carbon, filtered when hot, and the filtrate is cooled. The obtained shiny precipitate fatty to the touch is filtered off, washed with 80% acetic acid, and dried in a vacuum desiccator. 19.0 g. of the title compound are obtained; m.p.: 85—86°C (after recrystallization from absolute alcohol).

Example 11.

7-Cetyloxy-8-morpholinomethyl-isoflavone and salts

A mixture of 15.6 g. of 7-cetyloxy-8-chloromethyl-isoflavone, 50 ml. of absolute ethanol and 10 ml. of morpholine is refluxed for 6 hours. The solid substance slowly dissolves. The red solution is clarified with charcoal when hot, filtered, the filtrate is cooled and then it is immersed into a salty ice bath. The separated crystals are filtered off, washed with absolute ethanol, and dried in a vacuum desiccator. 15.5 g. of 7-cetyloxy-8-morpholinomethyl-isoflavone are obtained; m.p.: 93—94°C.

7-Cetyloxy-8-morpholinomethyl-isoflavone hydrochloride

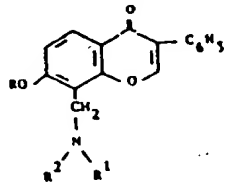
A mixture of 1 ml. of concentrated hydrochloric acid and 3 ml. of absolute alcohol is added to a hot solution of 11.0 g. of 7-cetyloxy-8-morpholinomethyl-isoflavone in 20 ml. of absolute alcohol. The clear solution is boiled for 0.25 hour, and then cooled. The separated salt is filtered off, washed with 96% alcohol, and dried. 6.3 g. of 7-cetyloxy-8-morpholinomethyl-isoflavone hydrochloride are obtained; m.p.: (151)—187—189°C.

7-Cetyloxy-8-morpholinomethyl-isoflavone nicotinate

A suspension of 1.3 g. of nicotinic acid in 5 ml. of isopropanol is added to a hot solution of 5.6 g. of 7-cetyloxy-8-morpholinomethyl-isoflavone in 28 ml. of isopropanol, and the mixture is boiled for 0.25 hour. The mixture is cooled, immersed into an ice bath, the separated crystals are filtered off, washed with isopropanol, and dried *in vacuo*. 4.8 g. of 7-cetyloxy-8-morpholinomethyl-isoflavone nicotinate are obtained; m.p.: (89—90)—97°C.

WHAT WE CLAIM IS: —

1. A compound of the general formula (I)



(I)

wherein
R is C_{1-18} alkyl, C_{2-18} alkenyl or C_{7-20} aralkyl,
R^1 is C_{1-4} alkyl, and
R^2 is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, phenyl, pyridyl or picolyl, or
R^1 and R^2 form together with the adjacent nitrogen atom a five- or six-membered heterocyclic ring with one or two hetero atoms,
or a physiologically acceptable salt thereof formed with an organic or mineral acid.

2. A compound according to claim 1 wherein R is C_{1-18} alkyl, vinyl, allyl, butenyl, octadecenyl, benzyl or β-phenethyl.

3. A compound according to claim 1 or 2 wherein R^1 and R^2 form together with the adjacent nitrogen atom piperazino, N-methyl-piperazino, morpholino, piperadino or pyrrolidino group.

4. A compound of the general formula (I), wherein
R is methyl, isopropyl or cetyl,
R^1 is methyl or butyl, and
R^2 is methyl, α-picolyl, α-hydroxyethyl or β-hydroxyethyl, or R^1 and R^2 form together with the adjacent nitrogen atom a morpholino, pyrrolidino or piperidino group, or a physiologically acceptable salt thereof.

5. 7-Methoxy-8-(methyl-β-hydroxyethyl-aminomethyl)-isoflavone and physiologially acceptable salts thereof.

6. 7-Methoxy-8-morpholinomethyl-isoflavone and physiologically acceptable salts thereof.

7. 7-Isopropoxy-8-morpholinomethyl-isoflavone and physiologically acceptable salts thereof.

8. 7-Isopropoxy-8-(methyl-β-hydroxyethyl-aminomethyl)isoflavone and physiologially acceptable salts thereof.

9. 7-Isopropoxy-8-piperidinomethyl-isoflavone and physiologically acceptable salts thereof.

10. 7-Isopropoxy-8-[n-butyl(2-methylpyrid-6-yl)-aminomethyl]-isoflavone and physiologically acceptable salts thereof.

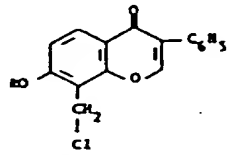
11. 7-Isopropoxy-8-pyrrolidinomethyl-isoflavone and physiologically acceptable salts thereof.

12. 7-Cetyloxy-8-morpholinomethyl-isoflavone and physiologically acceptable salts thereof.

13. The hydrochloride, hydrobromide, hydrosulfate, nicotinate, bitartrate, citrate, gluconate or lactate salt of a compound as claimed in any of claims 4 to 12.

14. Compounds according to claim 1, substantially as hereinbefore described with reference to any one of Examples 2, 3, 5—9 or 11.

15. A process for the preparation of a compound of the general formula (I) as defined in claim 1 which comprises reacting a compound of the general formula,



(III)

wherein R is as defined in claim 1 with a secondary amine of the general formula

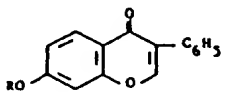
(IV)

wherein R^1 and R^2 each have the meanings defined in claim 1.

16. A process as claimed in claim 15, in which β-methylamino-ethanol, morpholine, piperidine, pyrrolidine or 2-n-butylamino-6-methylpyridine is used as amine reactant of the general formula (IV).

17. A process as claimed in claim 15 or 16, in which an alkanol of 1—4 carbon atoms or an excess of the amine reactant is used as reaction medium.

18. A process as claimed in any of claims 15—17 wherein said compound of the general formula (III) has been prepared by chloromethylating a corresponding compound of the general formula:—



(II)

19. A process as claimed in claim 18, in which the chloromethylation is performed with formaldehyde and concentrated hydrochloric acid in an acetic acid or propionic acid medium.

20. A process as claimed in claim 18 or 19, in which the chloromethylation is performed in the presence of a Lewis acid.

21. A process as claimed in claim 20 wherein said Lewis acid is zinc chloride, aluminium chloride or stannic chloride.

22. A process as claimed in any of claims 18—21, in which the chloromethylation is performed at 60 to 100°C.

23. A process as claimed in claim 22 wherein the chloromethylation is performed at 85 to 95°C.

24. A process as claimed in any of claims 15—23 including the step of converting the product of general formula (I) to a physiologically acceptable acid addition salt thereof.

25. A process as claimed in claim 15, substantially as hereinbefore described.

26. A process for the preparation of compounds of general formula (I) as defined in claim 1 and physiologically acceptable acid addition salts thereof, substantially as hereinbefore described with reference to any one of Examples 2, 3, 5—9 and 11.

27. Compounds of general formula I and physiologically acceptable acid addition salts thereof made by the process of any of claims 15—26.

28. A feed additive containing a compound as claimed in any of claims 1—4 or 13 as active ingredient and a physiologically acceptable carrier or comestible.

29. A feed additive as claimed in claim 28 comprising a compound according to any of claims 5—12 or 14.

30. An animal feed or watering composition comprising an anabolically effective amount of a compound as claimed in any of claims 1—4 or 13.

31. An animal feed or watering composition comprising an anabolically effective amount of a compound as claimed in any of claims 5—12 or 14.

32. A method of increasing the weight gain of livestock which comprises administering to said livestock an anabolically effective amount of a compound as claimed in any of claims 1—14.

33. A pharmaceutical composition containing as active ingredient a compound as claimed in any of claims 1—4, 13 or 14 together with a pharmaceutically acceptable solid or liquid carrier.

34. A composition as claimed in claim 33 comprising a compound according to any of claims 5—12.

35. A composition as claimed in claim 33 or 34 in unit dosage form.

For the Applicants,
FRANK B. DEHN & CO.,
Imperial House,
15—19 Kingsway,
London WC2B 6UZ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.